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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,700	02/09/2000	Carlos F. Barbas III	SCRIP1160-4	2975

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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	27

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/500,700	BARBAS III ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *2-5,16-19,40 and 42-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a supplemental amendment, filed 1/10/03 as Paper No. 25, in which applicants submitted a supplemental copy of the sequence listing, corresponding CRF and attorney's statement regarding the sequence listing. The application is now in sequence compliance.

The request filed on 5/28/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/500,700 is acceptable and a CPA has been established. An action on the CPA follows.

Receipt is acknowledged of a response, filed 7/9/02 as Paper No. 21, in which claims were cancelled without prejudice (claims 46-50) and in which several of the remaining claims were amended (claims 2-3, 16 and 42). Claims 2-5, 16-19, 40 and 42-45 are pending in the instant application. It is noted that the amendments to the claims specified in the non-entered amendment filed 2/28/02 as Paper No. 16 are identical to those presented in Paper No. 21. Thus, arguments presented in Paper No. 16 directed to the proposed claim amendments filed in Paper No. 16 regarding art rejections are relevant in the instant action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-5, 16-19 and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 21-22 and 53 of U.S. Patent No. 6,140,466. Although the conflicting claims are not identical, they are not patentably distinct from each other. **This rejection is maintained for reasons of record in Papers No. 6 and 10.**

Response to Arguments/ODP U.S. Patent No. 6,140,466

In Paper No. 16 applicants have again deferred response until such time as allowable subject matter is indicated. The rejection is maintained because the grounds for rejection remain.

Claims 2-5 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 22, 28-29, 31, 46 and 50 of U.S. Patent No. 6,242,568. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. **This is a new rejection.**

The instant claims are directed towards an isolated zinc finger-nucleotide binding polypeptide variant comprising at least two zinc finger modules wherein the amino acid sequence of at least one zinc finger module of the variant has at least one amino acid modification and wherein the isolated zinc finger-nucleotide binding polypeptide variant binds a DNA sequence different from one bound by zinc finger-binding polypeptide that doesn't have amino acid sequence modification and wherein the variant modules comprise two cysteine

residues amino-terminal to both histidine residues of the module. The variant can be derived from Zif268 or TFIIIA. The modules of the variant can be linked by the amino acid sequence TGEKP. The variant can be truncated.

Claim 1 is directed towards a method of isolating a zinc finger-binding nucleotide binding polypeptide variant that binds to a sequence different from that bound by the original zinc finger-binding nucleotide binding polypeptide. The zinc finger-binding nucleotide binding polypeptide used to produce the variant comprises at least two zinc finger modules wherein the amino acid sequence of each module that binds the DNA sequence comprises two cysteine residues amino terminal to two histidine residues. The other cited claims from the '568 patent are directed to variants, or the use of variants, that comprise the remaining limitations of the instant claims.

It would be prima facie obvious to practice the method of claim 1 in the '568 patent using Zif268 or TFIIIA as starting materials because the remaining claims make clear that the isolation of variants derived from these wildtype zinc finger proteins was contemplated by the inventors and was within the skill of the art. A variant obtained by the method of claim 1 would necessarily bind to a sequence not bound by another zinc finger-binding nucleotide binding polypeptide. Similarly, it would be obvious to use the method of claim 1 to obtain variants that comprise the TGEKP linker and/or are truncated, because the other cited claims from the '568 patent make clear that such variants are within the skill of the art and were contemplated by the inventors.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and

useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 40 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 46 of prior U.S. Patent No. 6,242,568. This is a double patenting rejection. **This is a new rejection.**

Claim 46 of the '568 patent recites that it is directed to a zinc finger-binding nucleotide binding polypeptide produced by the method of claim 36. It is noted, however, that claim 36 is actually directed towards an isolated variant of a zinc finger-binding nucleotide binding polypeptide and not to a method. The only method for producing a variant of a zinc finger-binding nucleotide binding polypeptide claimed in the '568 patent is that recited in independent claim 1. A review of the prosecution history of the application that issued as the '568 patent (08/676,318) indicates that the dependency of claim 46 was never adjusted to read on claim 1 (originally claim 36 in the application) at the time of allowance. Because claim 1 of the '568 patent recites each of the methods steps for the product-by-process composition of instant claim 40, and because claim 46 of the '568 patent should depend from claim 1 of the patent, claim 46 of the patent and instant claim 40 claim the same invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **The instant rejection is maintained for reasons of record in Papers No. 10 and 17. The original grounds of rejection in Paper No. 10 are summarized below.**

Claims 42-46 are directed towards a "hybrid" zinc finger protein that binds to a target nucleic acid, the hybrid zinc finger comprising zinc fingers from a first protein linked to zinc fingers from a second protein and whereby the hybrid protein binds a nucleic acid sequence different from that bound by any of the individual modules of the first and second proteins. A reasonable interpretation of the claim language includes embodiments wherein at least two zinc fingers from a zinc finger protein of one type (e.g. Zif268) and two zinc fingers from a protein of another type (e.g. TFIIIA). The fingers can be "variants" of the parental donor fingers. The "variants" can be mutagenized forms of the parental donor fingers. The hybrid zinc finger protein can modulate expression of the target nucleic acid. The amino acid sequence of each finger can comprise two cysteines and two histidines with both cysteines are amino proximal to both histidines. The rejected claims encompass an enormous genus of possible combinations of zinc finger modules obtained from literally any zinc finger protein that must retain the ability to bind a sequence different from a sequence bound by individual modules of the first protein and the second protein..

The specification exemplifies the zinc finger variants of the invention in terms of two known zinc finger proteins, Zif268 and TFIIIA. No other zinc finger proteins are described in detail in the specification. No description or relevant working example is provided wherein the zinc finger protein variant is a "hybrid" comprising fingers obtained from different types of proteins. In other words, no single embodiment of the claimed invention has been described in the specification. No significant description is provided of what such hybrid proteins would look like except to specify that the proteins would have zinc fingers obtained from different sources. The specification merely asserts that such recombinant hybrid proteins are feasible. No description is provided of which zinc finger modules from which sources would be desirable for recombination to produce a "hybrid" zinc finger protein. No description is provided of specific changes to generate "variants" that necessarily bind a given sequence that is not bound by a zinc finger nucleotide binding protein that lacks amino acid sequence modification. A single preferred linking domain, the 5 amino acid sequence TGEKP, is suggested for linking zinc finger modules in construction of the variant proteins of the invention. No other potential linking domain is described. No description is provided of other domains from any other zinc finger protein which would be retained in such any hybrid protein of the invention. Therefore, there is no basis provided by the specification for one of skill in the art to envisage a representative number of embodiments of the claimed invention that meet the functional limitations recited in the amended claims..

The prior art does not appear to rectify the deficiencies of the instant specification regarding the claimed invention. The claimed invention does not appear to have been described in the prior art. While zinc finger proteins are and were known in the art, the combination of

zinc finger modules to construct recombinant proteins does not appear to have been routinely practiced at the time of applicants invention. Nor does there appear to be a sufficient number of examples where "variant" zinc finger nucleotide proteins that retain an ability to specifically bind a given sequence that is not bound by a non-mutant zinc finger protein so that one of skill in the art has a structural/functional basis to envision those mutated variants that will meet the functional limitations of the claims.

Given the factors outlined above, one of skill in the art would not have been able to envisage a representative number of embodiments of such hybrid proteins or "variants" to describe the claimed genus that meet the functional limitations of the claims. Therefore, one of skill in the art would reasonably have concluded that applicants were not in possession of the claimed invention.

Response to Arguments/Written Description Claims 42-45

Applicant's arguments filed in Papers No. 16 and 21 have been fully considered but they are not persuasive. Paper No. 21 presents essentially the same arguments presented in Paper No. 16 and which were dealt with in the Advisory Action mailed 3/28/02 as Paper No. 17. The response to arguments made in Paper No. 17 are hereby incorporated and applied herein. To summarize, methods of screening to isolate the claimed hybrid zinc fingers that bind a particular sequence are not useful in allowing one to envision the exact primary structure of a given hybrid that will bind a given polynucleotide sequence. While it is true that the claimed zinc-finger proteins have a somewhat conserved modular structure, there remains no basis provided by the instant specification or prior art for one of skill in the art to envision which particular hybrid zinc finger protein will bind to a particular DNA sequence. Therefore, there is insufficient basis for

one of skill in the art to envision a sufficient number of hybrid zinc finger proteins that bind a particular DNA sequence so as to describe the broadly claimed genus of such hybrid proteins. The last paragraph of applicants' response in Paper No. 21 is unintelligible and can not be interpreted as written.

Claims 2-5, 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in Paper No. 21.**

Each of the claims comprises a new limitation wherein the claimed variant binds to a polynucleotide sequence different from a sequence bound by a zinc finger-binding protein not having amino acid sequence modification. As written, the limitation encompasses comparison to any zinc finger-binding protein in the art that differs in amino acid composition from the claimed variant. There does not appear to be support anywhere in the specification as originally filed for this limitation. Therefore, this limitation is impermissible NEW MATTER.

Claims 42-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in Paper No. 21.**

Each of the claims comprises a new limitation wherein the claimed hybrid variant binds to a polynucleotide sequence different from a sequence bound by individual modules of the first protein and second protein from which the hybrid is constructed. There does not appear to be support anywhere in the specification as originally filed for this limitation. Therefore, this limitation is impermissible NEW MATTER.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-5 and 42-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **The following are new rejections necessitated by applicants' amendment of the claims in Paper No. 21.**

Claim 2 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "zinc finger molecule" in line 6 of the claim. Does the term apply to the entire variant or just to one of the zinc finger "modules" of the variant?

Claim 42 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "zinc finger" in line 3 of the claim. Does the claim refer to a single module, or to the entire protein?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 2-5 and 16-19 comprise a new limitation wherein the claimed variant binds to a polynucleotide sequence different from a sequence bound by a zinc finger-binding protein not having amino acid sequence modification. As written, the limitation encompasses comparison to any zinc finger-binding protein in the art that differs in amino acid composition from the claimed variant.

Claims 2-5 and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanas et al (U; see the entire document). **This is a new rejection, necessitated by applicants' amendment of the claims in Paper No. 21.**

Hanas et al teach the construction and isolation of mutants of TFIIIA which either lack the fourth zinc finger module of TFIIIA (e.g. page 9862; Figure 1A) or comprise a fusion of the 7h and 8th modules (e.g. page 9862; Figure 1B). Hanas et al teach that both mutants retain the ability to bind their cognate binding sequence and influence transcription of a 5S RNA gene in Xenopus unfertilized egg extracts (e.g. Abstract; page 9866; Figures 4-5).

The modified variants taught by Hanas et al would not be expected by the skilled artisan to bind to the same polynucleotide sequences of an unrelated zinc finger protein (e.g. Zif268).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
March 10, 2003